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10/552,178	07/02/2007	**Masaaki Oka**	3462.1015-000	6214

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,178	OKA ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/3/10*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 7-17* is/are pending in the application.

4a) Of the above claim(s) *13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 5, 7-12, 16, 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/3/10 has been entered.

Claims 16-17 have been added by Applicant.

Claims 1, 2, 4, 5, and 7-17 are pending.

Claims 13-15 are withdrawn.

Claims 1, 2, 4, 5, 7-12, 16, and 17 are currently under consideration.

Rejections Withdrawn

The rejection under 35 U.S.C. 101 is withdrawn.

The rejection of claims 10, and 11 under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) is withdrawn.

The rejection of claims 10, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view

of Adorjan et al (US 2002/0192686 A1; 12/19/02) and further in view of Bloch et al (US 6,728,642 B2; 4/27/04) is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5 and 7-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) for the reasons stated in the Office Action of 3/10/10 and for the reasons set-forth below.

Okabe et al teaches a method of defining the differentiation grade of a tumor with genes selected by statistical analysis comprising determining the number of genes to define the differentiation grade of tumor and using microarrays based on expression level or pattern of genes of human liver tumor tissues, wherein the differentiation grade of tumor is non-cancerous liver, pre-cancerous liver, well differentiated HCC, moderately differentiated HCC, and poorly differentiated HCC and wherein the genes are differentially expressed between non-cancerous liver and pre-cancerous liver, precancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC

(see pages 2136-2137, in particular). Okabe et al further teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular).

Okabe et al does not specifically teach methods wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC. However, these deficiencies are made up in the teachings of Adorjan et al.

Adorjan et al teaches method of selecting cancer markers by using a Fisher ratio, referred to by Adorjan et al as a "Fisher criterion" (see paragraphs 0104-0105, in particular). Adorjan et al further teaches a Fisher ratio is a classical measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use any known calculation with the expression data of Okabe which would identify genes involved in carcinogenesis and tumor progression because Okabe motivates one to identify genes involved in carcinogenesis and tumor progression to further an understanding of the mechanisms of hepatocarcinogenesis, reveal novel

features of known genes, and identify biological factors involved in liver cancer (see right column of page 2129, in particular). Due to differences in results from each calculation which would identify genes involved in carcinogenesis and tumor progression, different calculations would result in different determinations of which genes are most important. Adorjan et al teaches method of selecting cancer markers by using a Fisher ratio, referred to by Adorjan et al as a "Fisher criterion" (see paragraphs 0104-0105, in particular). Adorjan et al further teaches a Fisher ratio is a classical measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). Therefore, it would be obvious to perform a Fisher ratio on expression data that has previously been examined with a Mann-Whitney test to identify genes involved in carcinogenesis and tumor progression, and vice-versa. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for identifying genes involved in carcinogenesis and tumor progression by performing Fisher ratios instead of the Mann-Witney test with the expression data of Okabe et al wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio in order to identify genes involved in carcinogenesis and tumor progression because Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular) and Adorjan et al teaches a Fisher ratio is a "classical" measure to assess the degree of

separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 6/3/10, Applicant argues that Okabe teaches genes associated with well differentiated HCC (G1) and genes associated with a combined group of moderately-to-poorly differentiated HCC (G2+G3), but does not teach the use of genes differentially expressed between "well differentiated HCC (G1) and moderately differentiated HCC (G2)". Applicant further argues that there is no motivation to use the Fisher ratio because the use of the Mann-Whitney test in the teachings of Okabe appears to be proper and complete. Applicant further argues that the claimed invention yields unexpected results because the claimed invention was able to identify genes that were not previously identified by Okabe. Applicant further indicates that Okabe et al does not disclose the five grades of tumors recited in claim 2.

The amendments to the claims and the arguments found in the Reply of 6/3/10 have been carefully considered, but are not deemed persuasive. In regards to the argument that Okabe does not teach the use of genes differentially expressed between "well differentiated HCC (G1) and moderately differentiated HCC (G2)", Okabe teaches determining gene expression in samples from well differentiated HCC (G1) and moderately differentiated HCC (G2) samples as claimed (right column of page 2136, in particular). Further, Okabe teaches selecting a set of genes associated with at least two

different grades of tumor differentiation - genes associated with well differentiated HCC (G1) and genes associated with a combined group of moderately-to-poorly differentiated HCC (G2+G3).

In regards to the argument that there is no motivation to use the Fisher ratio because the use of the Mann-Whitney test in the teachings of Okabe appears to be proper and complete, it is obvious to use any known calculation with the expression data of Okabe which would identify genes involved in carcinogenesis and tumor progression because Okabe motivates one to identify genes involved in carcinogenesis and tumor progression to further an understanding of the mechanisms of hepatocarcinogenesis, reveal novel features of known genes, and identify biological factors involved in liver cancer (see right column of page 2129, in particular). Due to differences in each calculation which would identify genes involved in carcinogenesis and tumor progression, different calculations would result in different determinations of which genes are most important. Adorjan et al teaches method of selecting cancer markers by using a Fisher ratio, referred to by Adorjan et al as a “Fisher criterion” (see paragraphs 0104-0105, in particular). Adorjan et al further teaches a Fisher ratio is a classical measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). Therefore, it would be obvious to perform a Fisher ratio on expression data that has previously been examined with a Mann-Whitney test to identify genes involved in carcinogenesis and tumor progression, and vice-versa.

In regards to the argument that the claimed invention yields unexpected results because the claimed invention was able to identify genes that were not previously identified by Okabe, the genes identified in the specification were identified using expression data from different patients than those of Okabe. One of skill in the art would recognize there are great differences in expression between patients, even those patients identified as being of the same differentiation grade. Due to differences in gene expression between patients, one would expect different patient populations to yield different results. Further, due to differences in results from each calculation which would identify genes involved in carcinogenesis and tumor progression, different calculations would be expected to result in different determinations of which genes are most important. Therefore, it is not surprising or unexpected that the specification identifies genes not identified by Okabe et al, and vice-versa.

In regards to the indication that Okabe et al does not disclose the five grades of tumors recited in claim 2, the method of Okabe et al uses non-cancerous liver, pre-cancerous liver, well differentiated HCC, moderately differentiated HCC, and poorly differentiated HCC (see description of "patients and Tissue Samples" on page 2129, in particular).

Claims 1, 2, 4, 5, and 7-9 remain and claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) as applied to

claims 1, 2, 4, 5 and 7-9 above, and further in view of Bloch et al (US 6,728,642 B2; 4/27/04).

The combined teaching of Okabe et al and Adorjan et al is discussed above.

The combined teaching of Okabe et al and Adorjan et al does not specifically teach a method wherein a minimum distance classifier with data of selected genes is designed and wherein a self-organizing map is generated with data of genes. However, these deficiencies are made up in the teachings of Boch et al.

Boch et al teaches a "minimum distance classifier" is a well-known cluster identification algorithm (see paragraph 0098, in particular). Boch et al further teaches illustrating classified genes into self-organizing maps (see Figures 10-11, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to design minimum distance classifiers with the genes identified by the Okabe et al and Adorjan et al and generate a self-organizing map with data of the genes identified by the method of Okabe et al and Adorjan et al because Boch et al teaches a "minimum distance classifier" is a "well-known" cluster identification algorithm (see paragraph 0098, in particular), Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular), and Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for designing minimum distance

classifiers with the genes identified by the Okabe et al and Adorjan et al and generate a self-organizing map with data of the genes identified by the method of Okabe et al and Adorjan et al because Boch et al teaches a "minimum distance classifier" is a "well-known" cluster identification algorithm (see paragraph 0098, in particular) and Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 6/3/10, Applicant repeats arguments that have been addressed above.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7-12, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **NEW MATTER** rejection.

Claims 1 and 10-12 recite methods wherein a Fisher ratio is determined without the use of a prior probability. Descriptions of methods wherein a Fisher ratio is determined without the use of a prior probability are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention. MPEP 2173.05(h) states that any negative limitation or exclusionary proviso must have basis in the original disclosure and any claim containing negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In the instant case, the negative limitation wherein a Fisher ratio is determined *without the use of a prior probability* does not have basis in the original disclosure.

In the Reply of 6/3/10, Applicant argues lines 27-32 at page 9 provide support for methods wherein a Fisher ratio is determined without the use of a prior probability.

The amendments to the claims and the arguments found in the Reply of 6/3/10 have been carefully considered, but are not deemed persuasive. In regards to the argument that lines 27-32 at page 9 provide support for methods wherein a Fisher ratio is determined without the use of a prior probability, lines 27-32 at page 9 do not provide support for methods wherein a Fisher ratio is determined without the use of a prior probability. There is no disclosure as to whether or not a prior probability is to be performed before a Fisher ratio is determined.

Claims 1, 2, 4, 5, and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) as applied to claims 1, 2, 4, 5 and 7-9 above, and further in view of Tang (World J Gastroenterol, 2001, 7(4): 445-454).

Okabe et al in view of Adorjan et al renders obvious claims 1, 2, 4, 5 and 7-9 (see above).

Okabe et al in view of Adorjan et al does not specifically render obvious methods wherein genes and/or proteins are selected that have the highest Fisher ratios in comparison between (1) non-cancerous liver and pre-cancerous liver, (2) pre-cancerous liver and well differentiated HCC tumor, (3) well differentiated HCC tumor and moderately differentiated HCC tumor, and (4) moderately differentiated HCC tumor and poorly differentiated HCC tumor. However, these deficiencies are made up in the teachings of Tang.

Tang teaches subjects with HCV expression in normal liver leads to HCC (see Abstract and right column on page 445, in particular). Tang further teaches motivation to identify biomarkers for HCC progression (see Abstract, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to select genes that have the highest Fisher ratios in comparison between (1) non-cancerous liver and normal liver expressing HCV (pre-cancerous liver), (2) pre-cancerous liver and well differentiated HCC tumor, (3) well differentiated HCC tumor and moderately differentiated HCC tumor, and (4) moderately differentiated HCC tumor and poorly differentiated HCC tumor when performing the combined method of

Okabe et al in view of Adorjan et al because Okabe et al teaches such tissues, Okabe et al teaches the importance of identifying genes involved in carcinogenesis and tumor progression, Tang teaches HCV expression in normal liver leads to HCC (see Abstract and right column on page 445, in particular), and each of said comparisons would identify genes involved in carcinogenesis and each step of tumor progression. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for selecting genes that have the highest Fisher ratios in comparison between (1) non-cancerous liver and normal liver expressing HCV (pre-cancerous liver), (2) pre-cancerous liver and well differentiated HCC tumor, (3) well differentiated HCC tumor and moderately differentiated HCC tumor, and (4) moderately differentiated HCC tumor and poorly differentiated HCC tumor when performing the combined method of Okabe et al in view of Adorjan et al because Okabe et al teaches such tissues, Okabe et al teaches the importance of identifying genes involved in carcinogenesis and tumor progression, and Tang teaches HCV expression in normal liver leads to HCC (see Abstract and right column on page 445, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 1, 2, 4, 5, 7-12, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) and in further view of Tang (World J

Gastroenterol, 2001, 7(4): 445-454) as applied to claims 1, 2, 4, 5, and 7-11 above, and further in view of Bloch et al (US 6,728,642 B2; 4/27/04).

Teaching of claims 1, 2, 4, 5, and 7-11 by the combined teachings of Okabe et al, Adorjan et al, and Tang is discussed above.

The combined teachings of Okabe et al, Adorjan et al, and Tang does not specifically teach method wherein a minimum distance classifier with data of selected genes is designed and wherein a self-organizing map is generated with data of genes. However, these deficiencies are made up in the teachings of Boch et al.

Boch et al teaches a "minimum distance classifier" is a well-known cluster identification algorithm (see paragraph 0098, in particular). Boch et al further teaches illustrating classified genes into self-organizing maps (see Figures 10-11, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to design minimum distance classifiers with the genes identified by the combined teachings of Okabe et al, Adorjan et al, and Tang and generate a self-organizing map with data of the genes identified by the combined teachings of Okabe et al, Adorjan et al, and Tang because Boch et al teaches a "minimum distance classifier" is a "well-known" cluster identification algorithm (see paragraph 0098, in particular), Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular), and Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular). One of ordinary skill in the art at

the time the invention was made would have had a reasonable expectation of success for designing minimum distance classifiers with the genes identified by the combined teachings of Okabe et al, Adorjan et al, and Tang and generate a self-organizing map with data of the genes identified by the combined teachings of Okabe et al, Adorjan et al, and Tang because Boch et al teaches a "minimum distance classifier" is a "well-known" cluster identification algorithm (see paragraph 0098, in particular) and Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642